REMARKS

Interview Summary

Applicants appreciate the opportunity provided by Examiners Mitchell and Guzo to confer regarding the meaning of the claims, the scope of the invention, and the distinctions between the prior art and the claimed subject matter. The current claims and remarks reflect the issues discussed in the interview of December 27, 2007.

Amendments

The claims have been amended for clarification purposes and to reduce and simplify the large claim set. Claim 90, previously indicated as allowable, has been amended to add the following recitations which rely on the following portions of the specification for support:

CLAIM 90 RECITATION	SPECIFICATION SUPPORT
wherein each window comprises a plurality of pieces and the pieces within a window are genomically clustered	A feature of the data analysis which enables the efficient practice of the method is the use of windows. These are groups of sequence tags which are genomically clustered. [22]

performing a plurality of comparisons for the plurality of windows	Top, middle and lower panels are similar to those for (Figure 3A) except that the bitmap viewer for chromosome 5 contains ~43,000 pixels, tag density values **were calculated in sliding windows** of 150 virtual tags, and yellow pixels indicate copy numbers >0.1 while black pixels indicate copy numbers ≤0.1. [12] A feature of the data analysis which enables the efficient practice of the method is **the use of windows**. These are groups of sequence tags which are genomically clustered. [22] Finally, tags are computationally extracted from sequence data, matched to precise chromosomal locations, and **tag densities are evaluated over moving windows** to detect abnormalities in DNA sequence content (Step 7). [25] **Tag densities were analyzed along each chromosome using sliding windows** containing 1000 virtual tags (~4 Mb), as windows of this size were predicted to reliably detect such alterations (Table 1). [28] To identify amplifications, which typically involve regions much smaller than a chromosomal arm, **average tag densities were dynamically calculated and visualized over sliding windows of different sizes**. Although some relatively small alterations could be detected using a 1000 virtual tag window (Fig. 2), **a window size of 50 virtual tags (~200 kb) was used for detailed analyses of amplifications** because it would be expected to provide a relatively high resolution and sensitivity for experimental data consisting of ~100,000 filtered tags (Table 1). [29] We next attempted to determine whether any deletions were present in DiFi cells. **Using a window size of 150 virtual tags (600 kb), we found evidence for four homozygous deletions** in the DiFi genome but none in the NLB cells. [31] Emphasis added.

New claims 92-103 have been added. They recite the features which are supported in the specification as follows:

CLAIMS	RECITATION	SPECIFICATION SUPPORT
92 and 104	pieces within the window map within 40 kb	Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb. Typically such windows comprise from 10 to 1000 sequence tags. [22]
93 and 105	pieces within the window map within 200 kb	Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb. Typically such windows comprise from 10 to 1000 sequence tags. [22]
94 and 106	pieces within the window map within 600 kb	Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb. Typically such windows comprise from 10 to 1000 sequence tags. [22]
95 and 107	pieces within the window map within 4 Mb	Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb. Typically such windows comprise from 10 to 1000 sequence tags. [22]
96 and 108	piece is defined by the presence of a BcgI restriction endonuclease recognition site which is flanked by 12 nucleotides on either end	In an alternative embodiment a single restriction endonuclease can define a defined portion of the genome. A fixed number of nucleotides on one or both sides of the restriction endonuclease recognition site then forms the sequence tags. For example, the restriction endonuclease *Bcg*I can be used to provide a 36 bp fragment. The 12 bp recognition site (having 6 degenerate positions) lies in the middle of a fragment; 12 bp flank the site on either side. [20]
97 and 109	identifying aneuploidy if (a)	Changes in amount of particular regions of

CLAIMS	RECITATION	SPECIFICATION SUPPORT
	pieces of one or more autosomes are determined to be present in the test eukaryotic cell relative to the reference eukaryotic cell at a ratio of 1.5 or greater or less than 0.7; or (b) pieces of one or more sex chromosomes in a male are determined to be present in the test eukaryotic cell relative to a reference male eukaryotic cell at a ratio of 1.5 or greater or less than 0.7; or (c) pieces of X chromosomes in a female are determined to be present in the test eukaryotic cell relative to a reference male eukaryotic cell at a ratio of 3 or greater or less than 1.5 or relative to a reference female eukaryotic cell at a ratio of 1.5 or greater or less than 0.7.	the genome can identify aneuploidy if (a) sequence tags of one or more autosomes are determined to be present in the test eukaryotic cell relative to the reference eukaryotic cell at a ratio of 3 or greater or less than 1.5; or (b) sequence tags of one or more sex chromosomes in a male are determined to be present in the test eukaryotic cell relative to the reference eukaryotic cell at a ratio of 1.5 or greater or less than 0.7; or (c) sequence tags of X chromosomes in a female are determined to be present in the test eukaryotic cell relative to the reference eukaryotic cell at a ratio of 3 or greater or less than 1.5, or relative to a reference female eukaryotic cell at a ratio of 1.5 or greater or less than 0.7. [23]
98 and 110	pieces representing less than 15 %	Thus, far less than 100 % of the sequence tags must be counted to obtain useful information. In fact, less than 50 %, less than 33 %, less than 25 %, less than 20 %, even less than 15 % of the sequence tags calculated to be present in the genome of the eukaryotic cell need be enumerated to obtain useful data.[22]
99	changes in copy number of portions	Changes in copy number of portions of the genome can be determined on a genomic scale. [15]
99	wherein each window comprises a plurality of pieces and the pieces within a window are genomically	A feature of the data analysis which enables the efficient practice of the method is the use of windows. These are groups of sequence tags which are genomically

CLAIMS	RECITATION	SPECIFICATION SUPPORT
	clustered;	clustered. [22]
100	gain or loss of a whole chromosome	Such changes include gain or loss of whole chromosomes or chromosome arms, amplifications and deletions of regions of the genome, as well as insertions of foreign DNA. [15]; *See also* Example 2: Analysis of whole chromosomes
101	a gain or loss of a chromosomal arm.	Such changes include gain or loss of whole chromosomes or chromosome arms, amplifications and deletions of regions of the genome, as well as insertions of foreign DNA. [15]; *See also* Example 3: Analysis of chromosomal arms
102	an interstitial amplification.	Whole chromosome changes, gains or losses of chromosomal arms, and interstitial amplifications or deletions can be detected. [16]; *See also* Example 4: Analysis of amplifications
103	an interstitial deletion.	Whole chromosome changes, gains or losses of chromosomal arms, and interstitial amplifications or deletions can be detected. [16]; *See also* Example 5: Analysis of deletions

Several of the claim limitations recited in the dependent claims correspond to subject matter which was previously identified as allowable. These include the recitations: pieces within the window map within 200 kb (Claim 93 and 105); piece is defined by the presence of a BcgI restriction endonuclease recognition site which is flanked by 12 nucleotides on either end (Claim 96 and 108); identifying aneuploidy if (a) pieces of one or more autosomes are determined to be present in the test eukaryotic cell relative to the reference eukaryotic cell at a ratio of 1.5 or greater or less than 0.7; or (b) pieces of one or more sex chromosomes in a male are determined to be present in the test eukaryotic cell relative to a reference male eukaryotic cell at a ratio of 1.5 or greater or less than 0.7; or (c) pieces of X chromosomes in a female are determined to be

present in the test eukaryotic cell relative to a reference male eukaryotic cell at a ratio of 3 or greater or less than 1.5 or relative to a reference female eukaryotic cell at a ratio of 1.5 or greater or less than 0.7 (Claim 97 and 109); and pieces representing less than 15 % (Claim 98 and 110).

It is respectfully submitted that no new matter is added by this amendment.

The Rejection of Claims 22 and 39 Under 35 U.S.C. § 112, first paragraph

Claims 22 and 39 have been cancelled but similar subject matter is recited in new claims 96 and 108. The rejection related to the recitation of two restriction sites defining a fragment when BcgI fragments only contain one BcgI recognition site. It is respectfully submitted that this issue is obviated in claims 96 and 108 which clearly define the presence of a BcgI site with flanking nucleotides.

It is respectfully submitted that this rejection does not apply to new claims 96 and 108.

The Rejection of Claims 6-9, 21, 43-46, and 56 Under 35 U.S.C. § 103(a)

Claims 6-9, 21, 43-46, and 56 were rejected but have now been cancelled, rendering the rejection moot. These claims were rejected over a combination of Velculescu[1], Dunn[2], and Yoshida[3].

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Velculescu teaches a means for generating sequence tags from mRNA and quantitating the sequence tags individually to determine and quantify expression of individual mRNAs. Only ~18 % of the tags calculated to be present are allegedly analyzed.

Dunn teaches a method of karyotyping a genome of a cell (exemplified by a prokaryotic

[1] U.S. Patent 6,498,013
[2] Genome Research, Vol. 12, Issue 11, 1756-1765, November 2002
[3] US Patent Application 2002/0147549

cell) in which number of copies of individual tags in a test cell are compared to the number of copies of those individual tags in a reference cell. Thus a tag-by-tag comparison is performed. *After* the tag-by tag comparison was performed, Dunn analyzed his data for the absence of adjacent tags. "Analysis of our data for the absence of adjacent tags revealed several places where deletions must have occurred in the EV766 genome." Page 1760, first column, lines 12-16. These are shown in Table 3, consisting of deletions comprising 25, 7, and 3 tags.

Yoshida is cited as teaching that *Not*I restriction endonuclease is methylation sensitive.

Amended claim 90 and new claim 99 recite:

> "…enumerating the pieces within a plurality of windows of fixed size of the genome, wherein each window comprises a plurality of pieces and the pieces within a window are genomically clustered;
>
> performing a plurality of comparisons for the plurality of windows in which a first number of pieces enumerated within a window for the test eukaryotic cell is compared to a second number of pieces enumerated within the window for a reference eukaryotic cell…."

Neither Velculescu nor Dunn teach the use of a plurality of windows of fixed size which comprise a plurality of genomically clustered pieces. Neither Velculescu nor Dunn teach performing a plurality of comparisons between such windows in a test and a eukaryotic cell. Thus neither of these references teach an essential element/step of the claim.

Even if, *arguendo,* one were to assert that Dunn's deletions represent windows, they are not windows of the genome of fixed size, as required by the claims. Moreover, Dunn does not teach performing a plurality of window-by window comparisons, as required by the claims.

Neither Velculescu nor Dunn teach the use of any windows of a plurality of genomically clustered tags within which pieces were counted and between which comparisons were made. *A fortiori* they do not teach such a window that spans 40 kb, 200 kb, 600 kb, or 4 Mb.

Yoshida does not remedy the deficiencies of the primary references in this regard.

For this reason, the rejection must fail if applied to claim 90 as amended and new claim 99.

The Rejection of Claims 16 and 53 under 35 U.S.C. § 103(a)

Claims 16 and 53 have been cancelled, rendering the rejection moot. The claims were rejected over the same two primary references, Velculescu and Dunn, further in view of Mohammed[4]. Mohammed is cited as teaching that diseases are associated with karyotypes and that determining karyotypes can be helpful to determine causality, diagnosis, or prognosis of a condition associated with a genetic defect, such as a hereditary disorder.

Mohammed does not remedy the deficiency of the primary references in teaching the use of a plurality of windows to compare two cells' genomes, wherein the windows are of a fixed size, comprise a plurality of pieces, and the pieces within a window are genomically clustered. Thus this three-way combination of prior art does not render obvious independent claims 90 or 99 or their dependent claims. This combination of references should not be applied to the pending claims.

The Rejection of Claims 17 and 54 under 35 U.S.C. § 103(a)

Claims 17 and 54 were rejected over a combination of the same two primary references, Velculescu and Dunn, further in view of Davis[5]. These claims are now cancelled, rendering the rejection moot.

Davis is cited for teaching the usefulness of analyzing a genotype for the existence of an allele or mutation responsible for a disease state. Such a teaching does not in any way remedy the deficiencies of the primary references, detailed above. Thus this combination of references is no more applicable to the current set of pending claims than those discussed above. This current set of references should not be applied to the pending claims.

The Rejection of Claims 19 and 55 under 35 U.S.C. § 103(a)

Claims 19 and 55 were rejected over the same two primary reference further in view of Winkfein[6]. These claims have been cancelled, rendering the rejection moot.

Winkfein is cited as teaching the use of the restriction endonuclease *Sac*I to analyze fetal

[4] U.S. Patent Application 2003/0124584
[5] U.S. Patent 5,391,480
[6] U.S. Patent 5,663,048

cells. Winkfein does not, however, remedy the deficiency of the primary references in teaching and using the windows as recited in independent claims 90 and 99. Thus this combination is no more pertinent to the pending claim set than the ones previously discussed above. This combination should not be applied to the current set of claims.

The Rejection of Claims 22 and 39 under 35 U.S.C. § 103(a)

Claims 22 and 39 are rejected over a combination comprising the same two primary references further in view of Israel[7]. These claims have been cancelled, rendering the rejection moot. In addition, the combination of references should not be applied to the current set of pending claims, claims 90 and 99 and their dependents, because Israel does not cure the deficiency of the primary references in teaching all elements of the claims.

Israel is cited as teaching the use of the restriction endonuclease *Bcg*I to fragment the genome and dimerizing the resulting fragments. This teaching in no manner remedies the deficiencies of the primary references. Thus this combination of references should not be applied to the pending set of claims.

Conclusion

Applicants respectfully request that the patentability of the current set of claims be considered. Applicants request that the next communication from the Patent Office be a Notice of Allowance.

Respectfully submitted,

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[7] U.S. Patent 5,981,190